

**REMARKS**

***Claim Amendments***

The text and status of all pending claims is set forth above, and the status of cancelled claim 10 is indicated in accordance with the new procedures. Only claims 1 and 4 are *currently amended* in substance. However, in order to avoid any misunderstanding, claims 3, 5, 6, 7 and 9 as set forth above have the original, unamended text, but have been reformatted with hanging indented paragraphs, to be consistent in format with claim 1.

Claim 1 has been amended to remove “amino” from the scope of R<sup>1</sup> and to delete a redundant exception at the end, and claim 4 has been made dependent on claim 1, to correct an error noted by the Examiner. The reasons for these amendments are more fully described below. No new matter has been added, and entry thereof is believed to be in order and is respectfully requested.

***Restriction Requirement/Election***

In response to the telephone restriction requirement of January 16, 2003, applicants elected the invention of Group I, and the claims were amended to be consistent therewith in the Preliminary Amendment filed on January 23, 2003, with confirmation of the election.

***Claim Rejections – 35 U.S.C. § 112***

The rejection of claim 4 under section 112 as being indefinite with respect to it appearing to be in independent form has been corrected by the above amendment to claim 4 by which claim

4 has been made dependent on claim 1, as suggested by the Examiner. This ground for rejection, therefore, has been overcome.

***Claim Rejections – 35 U.S.C. § 102***

Claim 13 has been rejected as being anticipated by Thompson *et al.* on the ground that the single compound recited in method of treatment claim 13 is disclosed in Thompson (compound no. 7z in Table 1, page 3782), and the assertion that both Thompson and method claim 13 are directed toward the treatment of malignant diseases. This ground for rejection is respectfully traversed in that the Examiner has incorrectly characterized the disease or medical condition treated by the method of claim 13.

Claim 13 is directed toward the treatment of a disease or medical condition mediated by *cytokines*, by administration of the recited compound. The Thompson reference, on the other hand, teaches certain compounds said to have *tyrosine kinase* inhibitory properties, in context of the role of EGF receptors in malignant diseases. The Thompson reference has no disclosure of the compounds being useful in the treatment of disease or medical conditions mediated by *cytokines*.

However, in order to make a connection between the method of claim 13 and the Thompson disclosure, the Examiner cites the specification at page 2, lines 15-16 as constituting an acknowledgement that cytokines mediate “malignant disease” and “tumour invasiveness and tumour metastasis.” However, in making this observation, the Examiner has overlooked the qualifying phrase at line 15, “**the cachexia found in** certain chronic diseases such as malignant disease, ... tumour invasiveness and tumour metastasis ...” (emphasis added). Cachexia is

defined, for example in Stedman's Medical Dictionary, as a general weight loss and wasting occurring in the course of a chronic disease or emotional disturbance. This weight loss and wasting *accompanying* certain chronic illnesses, such as cancer, is thought to be a result of over expression of cytokines due to the underlying disease. Thus, contrary to the Examiner's assertion, the specification is not here asserting that inhibition of cytokines *per se* treats cancer, but rather that it treats the cachexia that may result as an associated effect of cancer.

It is therefore respectfully submitted that the claim 13 method of treatment of a disease or medical condition mediated by cytokines is not disclosed or otherwise anticipated by the Thompson reference. Accordingly, this ground for rejection should be withdrawn.

***Claim Rejections – 35 U.S.C. § 103 - Thompson***

Claims 1, 9, 10 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Thompson, taken alone, again citing Thompson compound no. 7z in Table 1, page 3782. The Examiner recognizes that this compound is expressly excluded from the scope of the claims, but asserts that other compounds within the scope of the rejected claims are homologues thereof that differ by a  $-\text{CH}_2$  group noting, for example, that the 3-substituent on the phenyl ring can be  $-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{CH}_3$ , *etc.* The Examiner further notes that the reference teaches the compound is useful as a therapeutic agent for malignant diseases.

This ground for rejection is respectfully traversed, in that a *prima facie* case of obviousness has not been made out. Specifically there is no demonstration that persons of ordinary skill in this art would have been motivated to make the specific modification to the Thompson compound relied upon by the Examiner as supporting the rejection. The Examiner

relies only on the generalized concept of homology to support this rejection. However, more recent decisions of the Federal Circuit have cautioned against making generalizations from characterizations, such as isomers and homologues, as giving rise to *prima facie* obviousness.

See, for example, the Federal Circuit decision in *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985):

When chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made. See for example *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers); *In re Hoch*, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such "close" structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required.

Analysis of those circumstances in which a *prima facie* case has or has not been made in view of the degree of structural similarity or dissimilarity, or the presence or absence of similar utility between the prior art compound and that of the applicant, has inspired generations of applicants, courts, and scholars. Upon review of this history, we have concluded that generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other.

226 USPQ at 871-72 (emphasis added).

With respect to the present rejection, the Examiner cites Thompson compound 7z from Table 1, wherein the variable substituent "R" on the 4-anilino ring is 3'-NHAc, and asserts that the person of ordinary skill would be motivated to prepare structurally homologous compounds (-NH-C(O)-CH<sub>2</sub>-CH<sub>3</sub> *etc.*). However, it is submitted that such person would be motivated not to select compound 7z in the first place as the starting point for modification. Specifically, compound 7z, having an IC<sub>50</sub><sup>a</sup> (μM) of >10 is far less active than *most* other compounds on that table, and orders of magnitude less active than the authors' more preferred substituents, such as 3'-Br in compound 7f, having an IC<sub>50</sub><sup>a</sup> (μM) of 0.01. Therefore, applying the caution of the

Federal Circuit in *Grabiak*, this is a situation where an assertion of *prima facie* obviousness based upon only a generalization from homology should be avoided, in that there are other factors that contradict such a generalization.

Nevertheless, and in a sincere effort to advance the prosecution of this application to allowance, claim 1 has been amended to remove “amino” from the list of optional substituents for R<sup>1</sup>, thus even more clearly structurally distinguishing the present claims from the teachings of Thompson.<sup>1</sup> Thus, contrary to the presently claimed compounds, all compounds in Thompson Table 1 are **7-aminopyridolpyrimidines**.

Finally, the Examiner remarked with respect to this ground for rejection that the Thompson reference teaches the compound is useful as a therapeutic agent for malignant diseases. If the intended relevance of this remark is an implication that method of treatment claim 12 is also directed toward the treatment of malignant disease, the Examiner’s attention is respectfully called to the refutation of this same assertion with respect to the anticipation rejection of method of treatment claim 13, as discussed in the preceding section of these Remarks.

#### ***Claim Rejections – 35 U.S.C. § 103 -Ugarkar***

Claims 1, 9-10 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ugarkar *et al.*, WO 96/40706 (hereinafter “Ugarkar”) taken alone, which is asserted as teaching a generic group of compounds which embraces certain of applicant’s instantly claimed compounds. This ground for rejection is respectfully traversed.

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<sup>1</sup> The exception or proviso at the end of claim 1 has also been deleted by this amendment as being unnecessary, inasmuch as this compound is already excluded from the scope of this claim by reason of R<sup>1</sup> not being amino.

The Examiner has noted that there is some overlap in generic scope between the Ugarkar disclosure and claim 1, and cites the decisions of *In re Susi*, 169 USPQ 423 (CCPA 1971) and *Merck & Co. v. Biocraft Laboratories*, 10 USPQ2d 1843, 1846 (Fed. Cir. 1989) as holding that "a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus."

However, and contrary to the implication made by the Examiner, the Federal Circuit has more recently made very clear that inclusion of compounds within the scope a broad prior art genus does not render those compounds prima facie or structurally obviousness, particularly where the reference and/or the prior art as a whole bring the focus on other parts of that genus. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed.Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992)(Federal Circuit has ``decline[d] to extract from *Merck [ & Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d1843 (Fed. Cir. 1989)] the rule that . . . regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552,1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

It is also a fundamental principle of the patent laws that a *prima facie* case of obviousness has not been made unless it is demonstrated that persons of ordinary skill in this art would have been motivated by the prior art to select the particular claimed compounds or subgenus from the disclosed prior art genus. *In re Ochiai*, 71F.3d 1565, 1569-70, 37 USPQ2d 1127, 1131 (Fed. Cir. 1995); *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary

skill in the art."(emphasis in original)); *Jones*, 958 F.2d at 351, 21 USPQ2d at 1943-44 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897,1901 (Fed. Cir. 1990)(*in banc*); *In re Lulu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir.1984)("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.").

Thus, the Federal Circuit has specifically refuted the precise generalization for which the Examiner cites *Merck v. Biocraft*. Inclusion of compounds within a disclosed genus does not in itself give rise to a *prima facie* case of obviousness – there must be motivation in the reference or the art as a whole for persons of ordinary skill in the art to select from that broad genus the particular compounds of the present claims. It is submitted that such motivation is lacking here, where the preferences of the reference itself guide one away from the structure of the generic overlap.

In particular, there are almost two hundred examples in the Ugarkar reference, and the majority of the exemplified compounds have one or more halogen substituents on the 4-anilino ring. Moreover, Ugarkar specifically state on page 10, lines 6-7, that "[p]referably, X is a six member ring (phenyl), the most preferred substitution is at the para position, and the most preferred substituent is halogen (*e.g.* fluorine)." This clearly stated preference in the reference itself, combined with the direction of the exemplification, not only fails to motivate one skilled in the art to make the 3-aminobenzamide substitution of the present claims, but teaches away from doing so.

The Examiner also cites compound #129 (at page 24), having a 4-trifluoroacetamido substituent on the anilino group attached to the 4-position of the bicyclic ring system. The

Examiner acknowledges that this compound does not fall within the scope of the present claims, but asserts that present claims encompass structural isomers of compound #129. However, reference is again made to the Federal Circuit's admonition in *Grabiak* (cited and quoted above) that "generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other," as well as the well established requirement (as discussed above) that "the prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound." It is respectfully submitted that, upon consideration of the clear preferences verbally expressed in Ugarkar and the directions provided by the exemplified compounds, that one would not be motivated to select compound #129 as the starting point for modification, and even if one happened to do so, the motivation of the disclosure as a whole would be against making the "structural isomers" of the present claims.

Accordingly, a *prima facie* case of obviousness has not been made with respect to the Ugarkar reference, and it is respectfully requested that this ground for rejection be withdrawn.

***Claim Rejections – 35 U.S.C. § 103 -Wiesenfeldt***

Claims 1, 9 and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wiesenfeldt *et al.*, EP 447891 (hereinafter "Wiesenfeldt") taken alone, which is asserted as teaching compounds that are positional isomers of instantly claimed compounds. This ground for rejection is respectfully traversed.

As with compound #129 of the Ugarkar reference, the Examiner acknowledges that the structure of compound 249 of Wiesenfeldt is not within the scope of even the broadest genus of



the present claims, but is said to support a case of *prima facie* obviousness solely on the basis of it being a positional isomer of compounds that would be within the scope of the present claims. However, the Examiner has not cited any motivation to a person skilled in the art to select this particular compound and modify it so as to come within the scope of the present genus. To the contrary, it is respectfully submitted that the exemplification of Wiesenfeldt would motivate one away from selecting this particular compound 249 out of the 955 exemplified compounds for modification, and then to modify it in a manner that would bring it within the present claims. In particular, no other anilino is found within Wiesenfeldt's definition of  $R^2$  that has any substituent (at any position) that falls within the scope of the present claims. Thus, the circumstance where only one isolated compound out of over 900 compounds exemplifying a very broad genus does not even fall within the scope of the present claims but, at best, is asserted to be structural isomer, would itself teach the person of ordinary skill away from this isomer, and would provide no motivation to select *and* modify this single compound to come within the scope of the present claims.

Thus, again, the admonition of the Federal Circuit in *Grabiak* is noted, that "generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." Rather, as the more recent Federal Circuit cases noted above make clear, the prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound. Under the circumstances presented by the Wiesenfeldt reference as discussed above, it is respectfully submitted that such skilled person would not be motivated to select compound 249 for

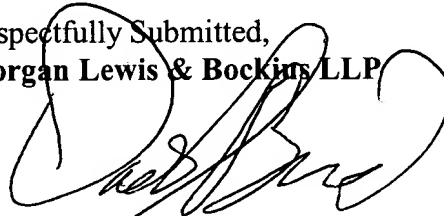
modification, and then modify this compound in a manner to come within the scope of the present claims.

Accordingly, a *prima facie* case of obviousness has not been made with respect to the Wiesenfeldt reference, and it is respectfully requested that this ground for rejection be withdrawn.

### ***Conclusion***

In view of the above amendments and the foregoing remarks, it is believed that all claims are in proper form, and that all grounds for rejection have been appropriately addressed and overcome. Accordingly, entry of these amendments, and the allowance of all claims, are respectively requested.

Respectfully Submitted,  
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